## REMARKS/ARGUMENTS

Reconsideration and allowance of the pending claims is respectfully requested in light of the remarks which follow. Claims 1, 11, and 46 have been amended. Claims 42 and 49-53 have been withdrawn as a result of a restriction requirement. Support for the amendment of claims 1, 11, and 46 can be found *inter alia* in the specification at page 19, paragraph [0061]. Claim 47 has been amended for consistency with the amendment to claim 46, and claims 33-36 and 38-44 have been canceled in light of the amendments to claims 1, 11, and 46. Upon entry of this amendment, claims 1-32, 37, 45-48, and 54-56 will be pending for examination.

### Restriction Requirement

Applicants acknowledge the Examiner's decision to make the restriction requirement final. Accordingly, claims 42 and 49-53 have been withdrawn from further consideration. Applicants expressly reserve the right under 35 U.S.C. § 121 to file a divisional application directed to the nonelected subject matter during the pendency of this application or an application claiming priority from this application.

### Double patenting rejection

Claim 11 stands provisionally rejected under 35 U.S.C. § 101 as allegedly claiming the same invention as claim 21 of copending Application No. 11/133,804 and claim 21 of copending Application No. 11/437,095. Applicants request that this rejection be held in abeyance until allowable subject matter has been identified in the one of the applications at issue here. Furthermore, Applicants have amended claim 11 to recite, in part, that "**X** comprises the sequence of SEQ ID NO: 1", thus distinguishing claim 11 of the present application from claim 21 of the copending applications.

### Claim rejections under 35 U.S.C. § 112, first paragraph - enablement

Claims 1-41, 43-48, and 54-56 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse.

In making this rejection, the Examiner appears to be essentially alleging (1) lack of enablement of prevention of diseases using the compositions of the invention and (2) lack of enablement of prevention of cellular uptake of portion **B** of the claimed compositions.

**A.** With respect to (1), the Examiner, for instance, states "[t]he art pertaining to the prevention of any condition (*i.e.*, cellular uptake) is highly unpredictable. Determining the various types or classes of conditions/diseases involving cells wherein cellular uptake is prevented requires various experimental procedures and without guidance that is applicable to all cells and conditions/diseases, there would be little predictability in performing the claimed invention". *See* Office Action at page 7. Applicants respectfully submit that the prevention of particular conditions or diseases is not a limitation recited in any of the claims. Rather, the claims generally recite the "prevent[ion] [of] cellular uptake of portion **B**", as a result of the linkage of portion **B** to an **A** portion comprising 2-20 acidic amino acids, which serves as a "veto" to prevent the uptake of **B** when linked to **A**. Accordingly, the Examiner's rejection based on alleged lack of enablement of disease prevention is simply inapplicable to the pending claims. For this reason, Applicants respectfully request withdrawal of this ground for rejection.

**B.** With respect to (2), the Examiner alleges "[t]he assumption that a peptide comprising a portion **A** that is about 2 to about 20 acidic amino acids linked by about 2 to about 100 atoms to a portion **B** that is about 5 to about 20 basic amino acid residues may be prevented from cellular uptake is an *incredible* finding for which Applicants have *not* provided supporting evidence. Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the complexes used in preventing cellular uptake as claimed." (Emphasis added.) *See* Office Action at page 7. Applicants respectfully disagree.

Contrary to the Examiner's allegation, the claim that an **A** portion comprising 2 to about 20 acidic amino acid residues is able to prevent the uptake of a linked **B** portion comprising about 5 to 20 basic amino acid residues is strongly supported by experimental data in the specification and, accordingly, the claims are not incredible. Specifically, Applicants direct the Examiner's attention to Examples 3 to 6 and Figures 7-11 of the specification, which provide ample evidence that an acidic amino acid containing portion **A** is able to prevent the uptake of a linked basic portion, **B**. Example 3 shows examples of 8 such peptide sequences (of the general

structure **A-X-B**) in which the linker **X** connecting **A** and **B** is cleavable by a protease, and **B** is labeled with a fluorescent marker (**B**-Fl) to allow the extracellular or intracellular localization of **B** to be determined. Example 5 and Figures 8-10 indicate that cleavage of the linker connecting **A** and **B**-Fl with a protease, thus eliminating the physical linkage of **A** with **B**-Fl, allows **B**-Fl to be taken up by cells as determined by FACS. In contrast, very little fluorescence is found to be associated with cells when uncleaved **A-X-B**-Fl peptide is incubated with cells, indicating the inability of the intact peptide to enter cells.

As a further demonstration, Example 5 and Figure 13 also shows the relative uptake of peptides of the general structure **A**-S-S-**B**-Fl, under reduced and non-reduced conditions. In this example peptide, the **A** and **B** portions are held together by a disulfide bond. Reduction of the disulfide bond results in release of the linkage between **A** and **B**-Fl. As indicated in Figure 13, reduction of the **A**-S-S-**B**-Fl peptide results in greatly increased accumulation of fluorescent signal inside cells as compared to cells incubated with the non-reduced peptide. Thus, an acidic **A** portion is able to prevent the uptake of a linked basic **B** portion, as claimed. In the words of the specification, "peptides having acidic portions [are able] to veto uptake". *See* specification page 34, paragraph [0096]. Furthermore, Examples 6 and 8 and Figure 15 of the specification provide examples of other peptides of the general structure **A-X-B** that may be used in the practice of the invention.

Moreover, Applicants have amended the claims to recite, in part, that "**X** comprises the sequence of SEQ ID NO: 1", a sequence which is cleavable by MMP-2. The amended claims are amply supported by evidence of enablement in Examples 4 and 5 and Figure 10 of the specification, which demonstrate that cleavage of an **A-X-B**-Fl peptide with MMP-2, when **X** is the sequence PLGLAG, results in a 10-20 fold increase in the uptake of **B**-Fl as compared with the uncleaved peptide.

Thus, contrary to the Examiner's allegation, Applicants assert that the claimed invention is enabled and that the specification "provide[s] competent evidence [and] disclosed tests that are highly predictive for the complexes used in preventing cellular uptake as claimed". *See* Office Action at page 7.

Finally, the Examiner has also alleged that the working examples do not enable the use of the claimed invention with the vast number of cell types that are known to exist. *See* Office Action at page 8. Applicants respectfully submit that the Examiner misunderstands the nature of the invention in raising this ground for rejection. In some embodiments of the invention, the fact that a given peptide of the structure **A-X-B** is cleaved by some cells but not others (thus allowing **B** to enter some cells but not others) forms the basis for the usefulness of some embodiments of the invention. Thus, in such embodiments, the usefulness of the invention lies in the specificity with which some cells (*e.g.*, cancer cells) are able to cleave **X**, thus freeing **B** from the inhibitory effect of **A** on **B**'s ability to be taken up by these cells, as compared to the lack of this ability in other cells (*e.g.*, non-cancer cells). Accordingly, claim 1, for example, recites that "**X** is a linker . . . joining **A** with **B**, which can be cleaved under physiological conditions, wherein **X** comprises the sequence of SEQ ID NO: 1". Not all cells will present the same physiological conditions that allow for peptide cleavage of **X**, which in this case is a site for cleavage by MMP-2. Thus, in the case of claim 1, while a peptide containing the linker **X** will only be cleaved under a specific set of physiological conditions (*e.g.*, those surrounding cancer cells that express MMP-2), the claimed invention will nonetheless be enabled for use with the "vast number of possible cell types known to exist" (a list of which is cited on page 8 of the Office Action) by virtue of the peptide not being cleaved by cells failing to exhibit the correct physiological conditions; this enables **A** to prevent the uptake of **B** at sites where the action of **B** is not desired, while promoting **B**'s uptake where needed.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

**Claim rejections under 35 U.S.C. § 112, second paragraph**

Claims 1-41, 43-48, and 54-56 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse.

**A.** In making the first part of this rejection, the Examiner alleges that claims 1-41, 43-48, and 54-56 are ambiguous "because it is unclear what linkers have about 2 to about 100 atoms which Applicant is referring to which can be cleaved under physiological conditions. In

other words, it is unclear what particular linkers Applicant is referring to that are compatible with the instant invention such that the desired results are yielded". *See* Office Action at page 9.

Applicants have amended claims 1, 11, and 46 to recite that "**X** comprises the sequence of SEQ ID NO: 1", a linker sequence that is cleavable by the metalloproteinase, MMP-2 (as shown, for example, in Example 4). These claim amendments render this ground for rejection moot; accordingly, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 112, second paragraph.

**B.** In making the second part of this rejection, the Examiner alleges that claims 1-41, 43-48, and 54-56 "are ambiguous because it is unclear what Xaa is in the sequences (SEQ ID NO: 13)." *See* Office Action at page 9.

To clarify, Applicants respectfully direct the Examiner to the specification on page 34, paragraph [0098], where SEQ ID NO: 13 is provided as $H_2N$-eeeeee-aca-PLGLAG-rrrrrrrr-aca-c(Fl)-$CONH_2$. (Underlining added.) Example 1 of the specification at pages 32-33, bridging paragraph [0092] indicates that the notation "aca=aminocaproic acid linker". By comparing the sequence of SEQ ID NO: 13 as provided in the specification with the sequence of SEQ ID NO: 13 as provided in the sequence listing, one sees that, in the sequence listing, Xaa stands in the position of the sequence that corresponds to the "aca", aminocaproic acid linker. Thus, the unknown or other amino acid denoted by Xaa (as per the convention set forth in 37 C.F.R. § 1.821) in SEQ ID NO: 13 of the sequence listing is aminocaproic acid. With this explanation, Applicants respectfully request withdrawal of this ground for rejection.

## CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,

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